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12 **PATENT APPLICATION** **A1**

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(54) **Film polymérique à base de prolamines, son procédé de préparation et ses applications .**

(57) Ledit film est constitué par un polymère hydrophobe comprenant:
(a) au moins une prolamine d'origine végétale,
(b) au moins un plastifiant choisi dans le groupe constitué par les hydrates de carbone et les esters tels que phtalates, adipates, sébaçates, phosphates, citrates, tartrates et malates, le rapport prolamine: plastifiant étant compris entre 2:1 et 2:0,5 et
(c) 5 à 30 % d'au moins un solvant choisi parmi les monools, les diols et l'eau.

(54) Prolamine-based polymeric film, process for preparing same and uses thereof.

(57) Said film consists of a hydrophobic polymer comprising:
(a) at least one prolamine of plant origin,
(b) at least one plasticizer chosen from the group consisting of carbohydrates and esters such as phthalates, adipates, sebacates, phosphates, citrates, tartrates and malates, the prolamine: plasticizer ratio being between 2:1 and 2:0.5, and
(c) 5% to 30% of at least one solvent chosen from monools, diols and water.

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The present invention relates to a polymeric film based on prolamines of plant origin, which can be used alone, as biodegradable material or as acceptable supports and/or vectors for active substances, and to uses thereof in the medical field, veterinary field, dietetic field, or the like.

Prolamines go to make up the composition of several cereals and in particular of wheat, rye, barley, oats, rice, millet and maize, with proportions which range between 0.1% (rice) and 3% (wheat).

In wheat, in particular, these prolamines contain a considerable proportion of nitrogenous amino acids and can be divided up into three classes:

- high-molecular-weight prolamines,

- sulfur-rich prolamines (α-, β- and γ-gliadins and subunits of 35 000 and 40 000),

- low-sulfur prolamines (ω-gliadins).

The applicant has given itself the aim of developing a film which can be used both as a biodegradable material and as a film which can be used as a support and/or vector for active substances, and which is of natural and plant origin, i.e. which does not have the drawbacks and risks, in particular in terms of virus transmission (mad cow virus, for example), of supports of animal origin, having a similar consistency, such as gelatin.

A subject of the present invention is a polymer-based film, characterized in that it consists of a hydrophobic

polymer comprising:

(a) at least one prolamine of plant origin,

(b) at least one plasticizer chosen from the group consisting of carbohydrates, preferably polyols and esters such as phthalates, adipates, sebacates, phosphates, citrates, tartrates and malates,

the prolamine:plasticizer ratio being between 2:1 and 2:0.5, and

(c) 5% to 30% of at least one solvent chosen from monools, diols and water.

As examples of monools and of diols, mention may be made of: methanol, ethanol, propanol, 2-propanol, butanol, pentanol, hexanol, ethylene glycol, propylene glycol or trimethylene glycol.

The prolamine according to the invention is preferably a native prolamine (i.e. not denatured), derived either from flour, or from fresh gluten of a cereal, such as wheat, maize, barley, oats or rye, preferably wheat or maize.

Such polymeric films based only on prolamine can be either in the form of a gel, or in the form of a dry film (sheet a few micrometers to a few millimeters thick, for example), depending on the degree of evaporation of the solvent.

These films, due to their high hydrophobicity, make it possible to prevent certain container-content interactions and can be used alone, as biodegradable material, or, in

combination with active substances, as a support or vector for said active substances.

In the pharmaceutical field in particular, such films (dry film or gel) have a texture which allows them to be administered orally, with the particularity of disaggregating slowly (dry film: between 5 minutes and 60 minutes, depending on the case) in the oral cavity or of dissolving slowly (gel); such films (dry film or gel) make it possible in particular to solve the problem of the oral administration of active substances, when swallowing problems exist, in particular in pediatrics, in geriatrics, or in dental surgery, compared with administration forms which must be swallowed or chewed.

Such films thus correspond better to the practical needs, in particular in that they can be combined with any active substance (hydrophilic or hydrophobic), are of plant origin, are of food quality (non-toxicity) and are biodegradable.

They also have a texture and mechanical properties (malleability, elasticity, non-adhesiveness, homogeneity) such that the films obtained can be used both as a biodegradable material (containers such as bin bags, disposable objects) and as a support in various types of industries, due to their hydrophobicity, in particular in paints, varnishes, etc., and also in dermocosmetics: transdermal systems, artificial skin, culture of fibroblasts

and keratinocytes, hair-removing film, sun gels, etc.

According to an advantageous embodiment of said polymeric film, the plasticizer is preferably chosen from glycerol, sorbitol, xylitol, neosorb® 70/70 (mixture containing at least 70% of sorbitol and of water, Roquette product), PEG 400 and PEG 1000.

Preferably, the plasticizer is glycerol, sorbitol or xylitol, or a mixture thereof.

According to a preferred arrangement of this embodiment, the plasticizer is a mixture of sorbitol and glycerol in proportions of between 2:1 and 2.5:1.

According to another advantageous embodiment of said polymeric film, it is formed from a starting liquid composition, which comprises:

- between 40% and 80% of at least one prolamine in solution in an aqueous-alcoholic solvent, the alcohol titer of which is between 40% and 80%, and
- at least one plasticizer, the plasticizer:alcoholic solution of prolamine ratio being between 0.10:1 and 0.50:1, preferably between 0.20:1 and 0.23:1.

By modifying the plasticizer:alcoholic solution of prolamine ratio, either a more or less brittle film (small amount of plasticizer), or a more or less flexible film (larger amount of plasticizer) is obtained. The more or less brittle film is in particular used in particulate form, whereas the more or less flexible film is used in the form of

a sheet and can be readily molded.

In accordance with the invention, the solvent is chosen from monools and diols, such as those defined above.

Unexpectedly, such polymeric films simultaneously have:

- specific mechanical properties: malleability, elasticity, and

- a homogeneous texture which is stable over time, thermoplastic and non-adhesive,

and which are particularly suitable for their use either in a solid galenic form (dry film), or in the form of a gel, for oral administration, by rapid disaggregation or dissolution in the oral cavity; in fact, despite the hydrophobicity of the film, the latter disaggregates or dissolves rapidly at acidic pH.

A subject of the present invention is also a process for preparing said polymeric film.

Said process comprises:

(a) adding at least one plasticizer, with stirring, to an aqueous-alcoholic solution of at least one cereal prolamine, at a temperature of between ambient temperature (18-20°C) and 40°C, and

(b) obtaining a gel.

According to an advantageous embodiment of said process, in order to obtain a dry film, the gel obtained in (b) is:

(c) spread over an appropriate support, and

(d) subjected to drying (stabilization and equilibrium of the product in relation to the environment: temperature, hygrometry).

According to another advantageous embodiment of said process, prior to step (a), the prolamines are advantageously extracted from the cereal flour or fresh gluten by:

- extracting using an aqueous-alcoholic solvent, the alcoholic titer of which is between 40% and 80%, at a temperature of between ambient temperature and 40°C,

- separating the solid phase and the liquid phase,

- concentrating, with respect to prolamines, the liquid phase obtained and obtaining an aqueous-alcoholic solution containing 50% to 80% of prolamines.

According to another advantageous embodiment of said process, the drying step (d) is carried out at a temperature of between 20°C and 26°C, and at a relative humidity of between 50% and 75% (atmosphere in which the water content is 11 g/m^3 of air).

According to another advantageous embodiment of said step (d), said drying is carried out at a temperature of between 55°C and 65°C and at a relative humidity of between 2% and 10% (atmosphere in which the water content is 2 g/m^3 of air).

In accordance with the invention, the drying step lasts between 16 and 70 hours.

As a variant, when the aqueous-alcoholic solution of prolamine is not used immediately for preparing the polymer, it can be stored, after evaporation, in the form of a powder, and can then be redissolved in an aqueous-alcoholic solution at the time of preparation of the polymer.

The subject of the present invention is also a composition, characterized in that it comprises a film (dry film or gel) as defined above, combined with at least one active substance.

For the purpose of the invention, the term "active substance" is intended to mean equally a chemical substance (paint, varnish, etc.), a biological substance (cells, such as fibroblasts, etc.), an active ingredient (medicament), a dietetic substance, a "cosmetological" substance (sunscreen, hair-removing substance) or a food product.

Such a composition can be:

- in the form of granules or of blocks of varying size and weight, depending on the desired use, in the case of a dry film, or

- in the form of gels.

Such compositions (dry film or gel) are particularly suitable for uses in the medical, cosmetics, agrofoods or agronomic field, which require the use of nontoxic, biodegradable polymers based on a solid support which can be molded.

In addition, and unexpectedly, such a film, when it is used as a pharmaceutical vector, has an effect on the bioavailability of the active substance which is combined with it (delay effect).

By way of nonlimiting examples, mention may be made of:

* as uses of the film according to the invention, in the form of a composition (film combined with at least one active substance):

- medical field: vector for a medicament for oral or transdermal administration, dermal gel, oral gel;

- dermocosmetological field: reconstituted skin, sun gel, hair-removing system;

- other field: cell culture support (combination with nutritive substances);

* as uses of the film according to the invention alone (i.e. not combined with an active substance):

- biodegradable materials.

Besides the above arrangements, the invention also comprises other arrangements which will emerge from the description which follows, which refers to examples of implementation of the process which is the subject of the present invention.

It should be clearly understood, however, that these examples are given only by way of illustration of the subject matter of the invention, of which they in no way constitute a

limitation.

EXAMPLE 1: Preparation of a film in accordance with the invention

A. Extraction of wheat gliadins:

A.1. Extraction from wheat flour:

a) 1 kg to 3 kg of wheat flour are added to 10 l of ethanol, the alcohol titer of which is 55%; the mixture is stirred for approximately 1 hour at 40°C.

b) The solid and liquid phases of the mixture obtained are separated by filtration or centrifugation; the supernatant is recovered, which supernatant contains gliadins at a concentration of approximately 5%.

c) This solution is concentrated a first time, by ultrafiltration, so as to obtain a gliadin-enriched solution (10-20%).

d) This solution is then concentrated by evaporation under a strong vacuum; this last step makes it possible to obtain a concentrated aqueous-alcoholic gel containing 50% to 80% of gliadins.

A.2. Extraction from fresh gluten:

a) 100 g of fresh gluten are added to 50 g of alcohol, under the same conditions as in step a) of A.1.

b) This step is identical to step b) of A.1.; however, an aqueous-alcoholic solution in which the gliadin concentration is approximately 20% is directly obtained, which makes it possible to avoid step c) of A.1.

d) This step is identical to step d) of A.1.

B. Preparation of the polymeric film

B.1. Polymeric gel:

- the plasticizer(s) is (are) added, with stirring, to the aqueous-alcoholic gel obtained in A. (A.1. or A.2.) and maintained at 40°C;

- after a few minutes, part of the alcoholic solvent having evaporated, the gel in accordance with the invention is obtained, and can be converted, if desired, into a dry film.

B.2. Production of a dry polymeric film in accordance with the invention by:

- spreading the gel over an appropriate support (support made of Teflon, polypropylene, glass or stainless steel),

- evaporating off the solvent, either at 24°C and at a relative humidity of 60%, for approximately forty hours or so, or at 60°C and at a relative humidity of 2%, for twenty hours or so.

Depending on the concentrations and the plasticizers used, the dry films, the compositions, mechanical qualities and texture of which are illustrated in the tables hereinafter, are obtained.

The meaning of the abbreviations in the tables hereinafter is as follows:

flex.: flexible; run.: running; shin.: shining; crack.: cracked; brit.: brittle; film.: film-forming; et.: ethanol; sol.: solution; tack.: tacky; rig.: rigid.

The degree of homogeneity is expressed in the following way:

+++: very homogeneous; ++: homogeneous; +: quite homogeneous; ±: only slightly homogeneous; -: only very slightly homogeneous (presence of lumps); 2-: non-homogeneous (presence of numerous lumps).

- The degree of clarity is expressed in the following way:

+++: very clear; ++: clear; +: quite clear; ±: only slightly clear; -: only very slightly clear; 2-: opalescent.

- The physical adhesion characteristic is expressed in the following way:

++: very adhesive; +: adhesive; ±: quite adhesive; -: only slightly adhesive; 2-: only very slightly adhesive; 3-: nonadhesive (removal of the film with little force).